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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,034	11/19/2003	Uri Herzberg	60004 (72021)	7145

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EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
02/16/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,034	HERZBERG ET AL.	
	Examiner	Art Unit	
	RENEE CLAYTOR	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,25-57 and 59-71* is/are pending in the application.

4a) Of the above claim(s) *1-6,25-42,53-57 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-52 and 60-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/28/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6, 25-57 and 59-71 are pending. Claims 1-6, 25-42, 53-57 and 59 are withdrawn from consideration and claims 43-52 and 60-71 are under examination herein.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/28/2010 has been entered.

Response to Arguments

Applicants argue over the 35 USC 112, first paragraph rejection. In particular, Applicants argue that the present specification discloses that other VR1 antagonists of Formula II are useful in the claimed methods and point specifically to [2-(2,6-dimethyl-morpholin-4-ylmethyl)-7-(3-trifluoromethyl-pyridin-2-yl)-pyrido[3,2-d]pyrimidin-4-yl]-(4-trifluoromethyl-phenyl)-amine in Example 12 as being useful in inhibiting the development of tolerance to repeated morphine dosing. Applicants also point to US Patent 7,074,799 to point out that a variety of compounds of Formula II are VR1 antagonists.

In response to the above arguments, while it is noted that three compounds of Formula II are exemplified in the present method, the above arguments are not considered persuasive. There are many different combinations of compounds of Formula II depending on what each substituent is in the formula. There are many different formulas that can be constructed via claim 43 given all the different chemical structures that can be applied to the substituents X, U, V, Z, Ar_1, W, Y and Ar_2. For example, there are many different combinations that can be applied to X, U, V, Z, W and Y which would lend to different compounds with different ring structures depending on the chosen substitution. Further, there are many different chemical structures that can be applied to Ar_1 and Ar_2. All of the various substitutions lead to very distinct compounds which leads to different bioavailabilities and reactivities of each compound. While there are three compounds of Formula II that are utilized in the treatment method in the specification, it is noted that the specification does not show a representative number of compounds of Formula II in the treatment method. It is noted that the compounds of Formula II may be VR1 antagonists as Applicants assert; however, it is noted that that does not mean that every compound of Formula II will show activity in the claimed method.

Applicants point out that claims 67-71 were not included in the rejection of which the Examiner acknowledges was an inadvertent error. The claims should have been rejected as the issues of enablement are the same for these dependent claims as applied to the independent claim 43 and are rejected accordingly herein.

Accordingly, the rejection is deemed proper and is maintained below.

Claim Rejections – 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-52, 60-71 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using ((6-trifluoromethyl-pyridin-3-yl)-[7-(3-trifluoromethyl-pyridin-2-yl)-quinazolin-4-yl]-amine, ([2-methyl-7-(3-trifluoromethyl-pyridin-2-yl)-quinazolin-4-yl]-(5-trifluoromethyl-pyridin-2-yl)-amine to treat tolerance to morphine, does not reasonably provide enablement for using all of the various compounds of Formula II to inhibit the development of tolerance to an opioid narcotic analgesic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7)

the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1) The nature of the invention and the breadth of the claims: The nature of the invention and breadth of the claims is a method for inhibiting the development of tolerance to an opioid narcotic analgesic comprising continuously or repeatedly administering to a patient simultaneously or sequentially in either order; (i) an opioid narcotic analgesic and (ii) a tolerance-reducing amount of a nontoxic VR1 antagonist represented by the formula (II).

2) The state of the prior art: The state of the prior art regarding compounds with core structures that overlap with the current Formula II is taught in Meyer et al. (US Patent 4,621,082) which teaches renal vasodilating and diuretic action. The art does not teach a host of compounds of Formula II in treatment of diseases, and in particular for inhibiting the development of tolerance to an opioid analgesic.

3) The amount of direction or guidance presented: The specification teaches the use of particular VR1 antagonists in the treatment method of the instant claims. In particular, Example 12 teaches inhibition of the development of tolerance to morphine analgesia in rats using the VR1 antagonist ((6-trifluoromethyl-pyridin-3-yl)-[7-(3-trifluoromethyl-pyridin-2-yl)-quinazolin-4-yl]-amine and ([2-methyl-7-(3-trifluoromethyl-pyridin-2-yl)-quinazolin-4-yl]-(5-trifluoromethyl-pyridin-2-yl)-amine which both showed an effect at treating tolerance to morphine analgesia. However, the results are not representative of all of the various possible formulations of Formula II. There are many possible substitutions of Ar_1, W, Y, Z, V, U, X and Ar_2 that will results in many different

compounds of Formula II, of which there is no indication that every compound will be effective in the method.

4) The quantity of experimentation necessary: "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed Cir. 1993)". Undue experimentation would be required in order to practice Applicant's invention because there are no examples provided in the specification. One would have to determine a useful model that correlates with clinical efficacy, a dosage range would need to be determined as well as a route of administration. Further, if any of the above failed, then the artisan would have to start over again in an effort to determine the suitable methods, dosage ranges and routes of administration in which to determine if the compounds will work to treat the disorders listed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RENEE CLAYTOR whose telephone number is (571)272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627